2022 New Year COVID Special

Talk of the Town

-A Midtown Journal Club Newsletter

Follower of Hieronymus Bosch, "Harrowing of Hell" (c. 1540-1560)
The world moves on in the face of the apocalypse.

How thin do we want the blood?

HEP-COVID and other trials provide conflicting results

Numerous cohort studies regarding the use of therapeutic versus prophylactic dose of heparins (unfractionated or low molecular-weight) have been published, but only a handful of randomized clinical trials have addressed whether therapeutic dose anticoagulants lead to decreased mortality and morbidity.

HEP-COVID was a multicenter, prospective, double-blinded randomized clinical trial involving 249 patients. Inclusion criteria were 1) requirement for supplemental oxygen, 2) plasma D-dimer level greater than 4 times the upper limit of normal or a sepsis-induced coagulopathy score of 4 or greater. Those requiring full-dose anticoagulation or dual antiplatelet therapy, bleeding within the past moth, active cancer/bronchiectasis/hepatic/renal dysfunction, thrombocytopenia/history of HIT were excluded.

The study compared Enoxaparin 1mg/kg SQ BID vs prophylactic unfractionated heparin or enoxaparin dosed per local institutional standards. Therapetic dose enoxaparin was associated with a **lower risk** of venous thromboembolsim (VTE) or arterial thromboembolism (ATE) (RR 0.37 [0.21-0.66], p<0.001). However, there was no signficiant difference in rate of death from any cause (RR 0.78 [0.49-1.23], p=0.28). Patients who did not require ICU level of care had lower rates of VTE, ATE, or death when they were on therapeutic enoxaparin (RR 0.46 [0.27-0.81], p=.004) but no significant difference was seen when stratified for ICU patients (RR 0.92 [0.62-1.39], p=0.71).

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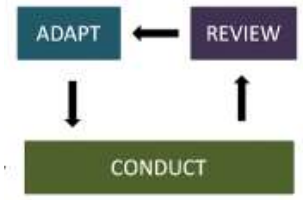


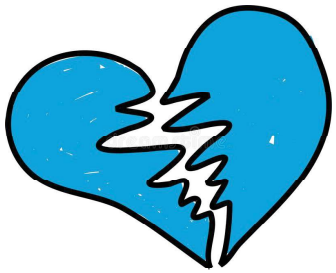
On the other hand, a recently published **open-label, adaptive multiplaform RCT** showed unclear benefit for the use of therapeutic anticoagulation. The study incorporated three simulataneously run trials (**REMAP-CAP**, **ACTIVE-4a**, and **ATTACC**), each allowing the update of randomization probabilities based on interim results. The studies' intervention arm was also heterogeneous that it allowed both LMWH and UFH.

Primary outcomes were available for a total of 1098 patients. There was no signficant difference in the rate of survival to hospital discharge (62.7% vs 64.5%, adjusted OR 0.84 [0.64-1.11], probability of futility (OR<1.2) 99.6%), number of organ support-free days (1 day vs 4 days, OR 0.83 [0.67-1.03]), and major thrombotic events or death (40.1% vs 41.1%, OR 1.04 [0.79-1.35]).

These results were again echoed in a recent meta-analysis involving 6 RCTs and 36 cohort studies by Zhang et al. involing 28,055 COVID patients, which did not show a difference in in-hospital mortality (RR 1.12 [0.99-1.25], p=0.06) and thrombotic events (RR=1.30 [0.79-2.15], p=0.30). Therapeutic anticoagulation did significantly increase bleeding risk (RR=1.66 [1.37-2.00, p<0.01). As of 1/1/2022, the NIH COVID treatment guidelines suggest that there is **insufficient evidence** to support higher than prophylactic doses of anticoagulation for admitted patients.

Article by Aleksan Khachatryan (PGY1), Siham Hussien (PGY1), Jeayoung Park (PGY2)

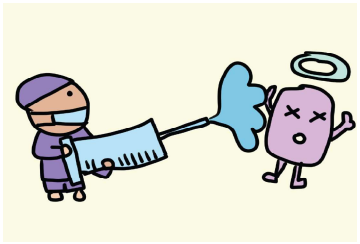
Heartbreaking Vaccine Fears!



In May 2021, the CDC issued a statement regarding a possible link between Pfizer and Moderna mRNA vaccines for COVID and **myocarditis**. This led to a fair amount of hubbub regarding the risk of myocarditis after receiving an mRNA vaccine for COVID-19 (at least on social media). However, many of the initial reports were case series that did not fully investigate the rate of this adverse event or describe the severity.

Article by Alex Gyftopoulos (PGY3)

Witberg et al. published a retrospective database review of myocarditis events after at least one dose of the Pfizer mRNA vaccine in the Clalit Health Services (HCO) in Israel. In the span of 5 months, around 2.5 million patients received at least one dose of the Pfizer vaccine, and 94% had received two doses. Of these individuals, 54 cases were identified as meeting the criteria for myocarditis with an estimated incidence of 2.13 cases per 100,000 persons. In a subgroup analysis, the highest risk was identified in male patients between age 16-29 with an estimated incidence of **10.69 cases per 100,000.** The vast majority of patients were hemodynamically stable and none required inotropes, vasopressors, or mechanical circulatory support on admission. Only one patient developed cardiogenic shock during their hospitalization requiring ECMO. Overall, myocarditis appears to be a **rare adverse event with most cases mild to moderate in severity,** with young males of age 16-29 at highest risk.



Rapid Review

New Therapies for Mild COVID Cases

With COVID-19 emerging into new variants, the need is rising for new methods to reduce the risk of discease progression. Currently **monoclonal antibodies** and **oral antiviral medications** are approved by the FDA for non-hospitalized patients, under Emergency Use Authorization (EUA).

There are three main monoclonal antibodies currently available as of 1/1/2022: 1) Eli Lilly's Bamlanivimab/Etesevimab (not approved in certain states due to resistance), 2) Regeneron's Casirivimab/Imdevimab, 3) GlaxoSmithKline's Sotrovimab. All three medications target the spike protein of the SARS-CoV-2 virus which attaches to the angiotensin-converting enzyme 2 (ACE2) of host cells. **Bamlanivimab/Etesevimab** are two antibodies that bind to two different but overlapping regions on the COVID spike protein, whereas **Casirivimab/Imdevimab** works on two different non-overlapping regions. Phase 3 of the REGEN-COV trial showed a decreased rate of hospitalization or death from any cause by day 29 (RRR 71.3% [51.7-82.9], p<0.001) as well as a decreased median time to resolation of symptoms (10 vs 14 days; p<0.001) with casirivimab/imdevimab given within 7 days of symptoms. There was no difference between 1.2g and 2.4g doses.

More recently **oral** antivirals, Paxlovid and Molnupiravir, have been approved for non-hospitalized patients with high risk of disease progression. In a recent study involving 1433 patients, a course of Molnupiravir 800mg twice daily for 5 days was shown to decrease rates of hospitalization or death by day 29 (6.8% vs 9.7%, mean difference -3.0% [-5.9, -0.1]). Time for symptom resolution was checked for individual symptoms, but was not found to have a significant difference. Currently the oral antivirals are approved for outpatient treatment only, and trials are ongoing to verify efficacy in post-exposure prophyalxis. (See Table 1) The oral medications may prove to be a valuable resource as it does not require special measures of storage/administration.

	Outpatient Treatment	Post-exposure Prophylaxis	Price
Bamlanivimab /Etesevimab	✓	✓	$1,250
Casirivimab /Imdevimab	✓	✓	$1,250
Sotrovimab	✓	✗	$2,100
Paxlovid (ritonavir)	✓	✗	$530
Molnupiravir	✓	✗	$700
Pfizer Vaccine			$20

Table 1. Emergency Use Indications and Price for monoclonal antibodies (green) and oral antivirals (blue) as of 1/1/2022. Pfizer vaccine included for comparison.

Article Contributed by Yazan Alzedaneen (PGY2), Elvina Yunasan (PGY1), Jeayoung Park (PGY2), Dena Tran (PGY3). Illustration by Harim Kim (PGY2)

Featured Meta-analyses

Prevalance and Outcomes of Acute Pancreatitis in COVID-19

In a recent publication on *Gut*, Yang et al. studied the prevalence and outcomes of acute pancreatitis (AP) in COVID-19. Eleven studies were included, of which six were multi-center and eight were retrospective. Overall pooled prevalence of AP in 88,635 patients with COVID-19 was 3.1% (95% CI 1.6-5.1%), and pooled mortality was 18.5% (95% CI 12.6-25.1%).

Patients with both AP and COVID-19 had a higher portion of males, unknown/idiopathic etiology, greater severity, increased risk of pancreatic necrosis, ICU admissions, persistent organ failure and need for mechanical ventilation compared to AP patients without COVID-19. The mortality rate was also higher. The study was limited by small number of included studies, lower even rates, and high levels of heterogeneity (I_2 =98% for pooled prevalence) due to differences in study design and methodology, but the presented study was the best available data at the time of publication.

Article by Yuting Huang (PGY3). Dr. Huang was one of the authors of the above study.

Editor's Commentary

Severe Concerns Raised over Ivermectin Studies

A few recent major meta-analyses (Bryant et al., *Am J Ther* 2021; Hill et al., *Open Forum Infectious Diseases* 2021) have reported significant benefits of ivermectin for COVID treatment, with reduced risk of death up to 38% (95% CI 0.19-0.73) in the Bryant et al. paper. These results have created a fervent, religious following of ivermectin as a "miracle" treatment, with prominent politicians and religious leaders publically endorsing the medication. Close scrutinity of the individual studies, however, raised significant concern over these rosy results. One RCT (Elgazzar et al., *Research Square* 2021, preprint, now retracted) which represented more than 10% of the overall effect was found to have serious concerns regarding its validity with evidence of data fabrication, and another RCT (Niaee et al., *Asian Pac. J. Trop. 2021)* raised concerns regarding randomization failure. Hill et al. published a revised analysis excluding the two studies and other studies with high risk of bias-- no significant difference in risk of hospitalization or survival was seen. A Cochrane review by Popp et al. additionally criticized the Bryant et al. meta-analysis because it included a very heterogeneous group of patients of different disease severities, duration of treatment, controls, and outcomes. It is very important for today's clinicians to develop a critical mindset when evaluating literature, with high volumes of research being published without close scrutiny.

<ToTT newsletter>
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